

Claims 13-36 are all pending claims. By this Amendment, claim 14 has been canceled without prejudice or disclaimer.

**I. Rejections Withdrawn**

The rejection of claim 26 under 35 U.S.C. 112, second paragraph, is withdrawn in view of Applicant's arguments on pages 2-3 in the Response filed on March 9, 2001.

The rejection of claim 36 under 35 U.S.C. 102(e) as being anticipated by Fukuda et al. (U.S. Patent No. 5,908,826, 1992) is withdrawn in view of Applicant's amendment thereto.

**II. Response to Rejection of Claims 13-21, 23-32, and 34-36 under 35 USC §103(a)**

Claims 13-21, 23-32, and 34-35 remain rejected and newly amended claim 36 is rejected under 35 U.S.C. §103(a) as being obvious over Phillips et al. (WO 89/11297) in view of Friedman et al. (U.S. Patent No. 5,750,142) and Arizono et al. (Arzneimittelforschung, Vol. 44, No. 7, 1994) for reasons of record.

The Examiner is not persuaded by Applicants' previous argument that the teachings of Friedman would not have been combined with Phillips at the time of the invention, and that the combination of the two references would not result in the present invention because Friedman discloses that the composition disclosed, **may** contain a suspending agent such as gelatin or pectin or polyethylene glycol. According to the Examiner, the disclosure by Friedman that the composition "may" contain a suspending agent, such as gelatin or pectin or polyethylene glycols (i.e., preferred embodiments), does not negate the combination of the references.

The Examiner is also not persuaded by Applicants' arguments that the composition of Friedman does not contain a carbohydrate, and that the reference dissuades their use. The previous rejection was not concerned with the presence or absence of a carbohydrate, but with the teachings of Friedman that the composition of Phillips could be optimized by adding at least one amino acid and a surfactant.

According to the Examiner, Friedman teaches the advantages of incorporating at least one amino acid and a surfactant since amino acids provide superior performance with respect to the droplet size of the reconstituted product (Friedman et al., col. 2, line 27) and the addition of surfactants can be used to enhance the formation of the emulsion (Friedman et al., col. 5, line 12).

Applicants traverse for the following reasons.

Phillips discloses a lyophilisate containing

- a buffer (page 6);
- a carbohydrate (page 5);
- a monoclonal antibody or fragment (page 5 and 6);
- residual moisture (pages 17-18);
- the lyophilisate being in the form of a cake (page 6);
- the formation of particles 10-25 microns in size and falling within USP limits (page 12-13); and
- the reconstituted lyophilisate being reduced in its dimerization of the protein (page 13).

Phillips does not teach or suggest an amino acid or a surfactant being added as auxiliary additives much less that these additives would affect the stability of the protein in the lyophilisate. Phillips is also silent with respect to an amino sugar and the species of

amino sugars claimed in claims 22 and 33. Accordingly, Phillips, alone, does not appear teach or suggest the instant claimed invention.

Example 3 of the specification elucidates the necessity of amino acids and a surfactant in the preparation of the invention. The use of sucrose as a stabilizer, alone, leads to an unstable lyophilisate. Phillips makes a general disclosure for a **carbohydrate** component (page 5), and sucrose is encompassed within the meaning of a carbohydrate. Even assuming that Phillips teaches sucrose within the meaning of a carbohydrate, Applicants demonstrate, unequivocally, that a formulation such as that described by Phillips and lacking amino acids, results in a less stable product.

Friedman discloses a lyophilisate composition containing an amino acid or an amino compound, a surfactant and a "**readily lipid soluble drug**". Friedman is silent with respect to antibodies and fragments thereof, for use as drugs in its disclosure of a lyophilisate. Friedman lists the lipophilic drugs starting at Col. 5, line 49- Col. 8, line 18, and the only protein agents include hemoglobin and hormones, neither of which class of compounds read on a monoclonal or polyclonal antibody of the instant claims. Applicants submit that soluble antibodies are hydrophilic or water soluble, and that an antibody might only be considered "lipophilic" when bound to a cognate antigen in association with a membrane complex.

Friedman also specifically excludes carbohydrates from the lyophilisate composition (Col. 3, lines 3-6), teaching that by excluding sugars, the composition advantageously reduces the risk of microbial growth (Col. 2, lines 5-9). By teaching away from the use of carbohydrates, Friedman does not provide any motivation to combine its lyophilisate composition with the composition of Phillips, since sugar is an essential component of Phillips composition. In fact, when the teachings of the prior art conflict as

in the present case, the burden rests on the Examiner to evaluate each reference and to consider the degree to which one reference accurately discredits another (*In re Young*, 18 USPQ2d 1089 (Fed. Cir. 1991)).

The Examiner's further reference to Arizono is also without merit. Arizono does not teach any more than what Phillips already teaches, so as for the Examiner's choice of a secondary reference, Arizono does not rectify the deficiencies of Phillips as a primary reference.

The Examiner has not established a *prima facia* case of obviousness for the claimed invention in view of the cited references alone or in combination. The cited references alone or in combination do not teach or suggest the instant claimed invention as a whole and for the reasons set forth below, their disclosures do not provide any motivation to combine them in the manner asserted by the Examiner:

- 1) the Friedman reference specifically teaches away from adding a carbohydrate to a formulation whereas Phillips teaches sugars as being essential to the stability of the lyophilisate; and
- 2) Friedman's lyophilisate is formulated for **lipophilic drugs** whereas the antibody of Phillips is lipophobic or hydrophilic.

Even when a combination of references teaches every element of the claimed invention, the references must also provide a motivation to combine them in order to support a *prima facia* case of obviousness (*In re Rouffet*, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998)). The Examiner has not established a *prima facia* case of obviousness for the very reasons that the references do not provide an inherent nor an implicit

motivation to combine their disclosures, and accordingly, withdrawal of the rejection is deemed proper.

### **III. Response to Objections to Claims 22 and 33**

Claims 22 and 33 remain objected to for depending from a rejected base claim.

Applicants submit that in view of the foregoing arguments urging patentability of the base claims from which claims 22 and 33 depend, that the dependency for these two claims be presently maintained.

### **IV. Response to Rejection of Claim 14 under 37 CFR §1.75**

Claim 14 is objected to under 37 C.F.R. §1.75 as being a substantial duplicate of claim 13.

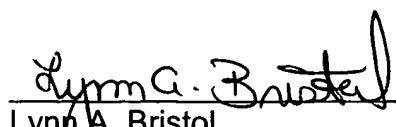
In view of the cancellation of claim 14, the Examiner's objection has been rendered moot.

### **CONCLUSION**

In view of all of the foregoing arguments and comments, Applicants submit that the application is now in condition for allowance and that the Examiner allow the application to pass to issuance.

The Commissioner is hereby authorized to charge any fee deficiency or credit any overpayment associated with this communication to Deposit Account No. 01-2300.

Respectfully submitted,

  
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